

## EDITORIAL

# New Horizons in Allergen Immunotherapy

Robert A. Wood, MD

**Even though allergen immunotherapy** has been studied for more than a century, a great deal remains unknown about this commonly used treatment.<sup>1</sup> Immunotherapy, which is of ben-



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efit to the majority of appropriately selected patients, still largely relies on the injection of relatively crude allergen extracts, often involving doses that have not been rigorously studied.<sup>2</sup> The renewed interest in the study of immunotherapy over the past decade is encouraging and has resulted in important advances, including development of more refined allergens, assessment of different routes of delivery, and studies on the treatment of food allergy.

In this issue of *JAMA*, Virchow and colleagues<sup>3</sup> report the results of a large, multicenter clinical trial using 1 of these newer approaches, referred to as sublingual immunotherapy (SLIT). The study focuses on house dust mite (HDM) allergen, an appropriate target for study given its importance as the allergen that is most often implicated as a trigger for asthma and perennial allergic rhinitis on a worldwide basis. Numerous studies have demonstrated the efficacy of subcutaneous immunotherapy (SCIT) using HDM allergen for both asthma and allergic rhinitis,<sup>4-6</sup> and a smaller number of studies have shown overall positive results using SLIT.<sup>7-11</sup> Data on use of SLIT in patients with asthma are still limited, however, and are of special interest because SLIT is associated with fewer adverse reactions, especially in patients with asthma, than SCIT.

Virchow and colleagues conducted a double-blind, randomized, placebo-controlled trial that included 834 adults with HDM allergy and asthma that was not well controlled with inhaled corticosteroids (ICS) or combination products. Patients with severe or unstable asthma, defined as a forced expiratory volume in the first second of expiration (FEV<sub>1</sub>) less than 70% of predicted value or hospitalization within the prior 3 months, were excluded. Participants were randomized to 3 treatment groups, including 1 of 2 doses of sublingual tablets of HDM allergen, 6 SQ-HDM (n = 275) or 12 SQ-HDM (n = 282) (the latter dose with twice the allergen biological activity of the former dose) or placebo (n = 277) delivered in a tablet form. Efficacy was assessed during the last 6 months of treatment when ICS doses were reduced by 50% for 3 months and then completely withdrawn for 3 months.

The primary outcome, defined as the time to the first moderate or severe asthma exacerbation during the ICS reduction, was improved by both doses of active SLIT compared with placebo, with hazard ratios of 0.69 (95% CI, 0.49-0.96) for the 6 SQ-HDM group and 0.66 (95% CI, 0.47-0.93) for the 12 SQ-HDM group. The absolute risk for first exacerbation was 26% (n = 62) for the 6 SQ-HDM group, 24% (n = 59) for the 12 SQ-HDM group, and 32% (n = 83) for the placebo group, primarily involving moderate rather than severe exacerbations, with

no significant difference between the 2 active treatment groups. Although mild to moderate adverse reactions were common, mostly related to oropharyngeal pruritus or irritation, there were no reports of severe systemic allergic reactions. The authors concluded that among adults with HDM allergy-related asthma not well controlled by ICS, the addition of HDM SLIT delivered as a once-daily tablet significantly prolonged the time to the first asthma exacerbation during ICS reduction.

As with any clinical trial, the critical question is how meaningful is this outcome. Can these results truly benefit similar patients encountered in clinical practice? Addressing these questions requires consideration of not just the primary end point but also the secondary outcomes and potential study limitations. With regard to secondary outcomes, there were significant differences favoring the active therapy compared with placebo when different criteria were used to define asthma exacerbations, as well as in immunologic changes consistent with desensitization. However, there were no significant differences in patients' responses to questionnaires regarding either asthma control or quality of life.

The authors addressed several study limitations, including that patients with more severe or unstable asthma were excluded from the trial. However, there are several additional concerns, including that "unblinding" may occur with SLIT administration, given the common occurrence of local adverse effects related to active treatment. In addition, because the study only included adults with HDM allergic asthma (mean age, 33 years [range, 17-83]), the findings cannot be generalized to children, in whom asthma exacerbations remain among the most common causes of emergency department visits and hospitalizations.

Despite these limitations, the results of the study by Virchow et al are important and clinically relevant. In particular, instead of the more common approach of studying patients with milder asthma or those with only allergic rhinitis, this trial focused on the more challenging subset of patients with asthma, those with inadequate symptom control despite treatment with ICS. The authors' choice of a primary end point based on exacerbations during ICS reduction is also unique to immunotherapy trials, with previous trials of HDM immunotherapy focusing on medication requirements, symptoms scores, or lung function as primary end points. Furthermore, the inclusion of moderate exacerbations in the primary outcome is also important, with even trials of asthma controller medications usually focusing only on severe exacerbations. Although it is possible to argue that severe exacerbations are the most clinically important end points, this study aimed to identify exacerbations before they developed into severe events, which are both costly and can be potentially life-threatening.

In addition, this study focused on a single allergen. Although treatment with a single major allergen, considered to be

most relevant for that individual patient, is the usual practice in Europe, this approach is not typical in the United States, where most immunotherapy is prescribed to include multiple allergens, directed at as many of the patient's specific sensitivities as possible. Most studies demonstrating the efficacy of immunotherapy have used single allergens, with considerably less data to support the multi-allergen approach. In this study, 66% of the participants were sensitized to other allergens in addition to HDM, with no differences in outcome detected between those patients and those monosensitized to HDM, demonstrating the clinical efficacy of single allergen immunotherapy even among polysensitized patients.

Aside from this ongoing question regarding single vs multi-allergen immunotherapy, what clinical issues and research questions remain to be addressed? Should SLIT replace SCIT as the mainstay of immunotherapy? Although direct comparisons are limited, SLIT appears to be overall somewhat less effective than SCIT.<sup>12-14</sup> However, SLIT offers several specific advantages over SCIT; it can be self-administered, requires little or no dose escalation, does not require injections, and carries a much lower risk of anaphylaxis. For seasonal allergens, SLIT has been shown to be effective when instituted prior to and continued throughout the pollen season, as opposed to the year-round injections required with SCIT. The main disadvantage of SLIT is that it requires adherence with daily dosing, and studies have consistently shown low rates of long-term adherence. For example, a review of published studies found that 55% to 82% of patients abandoned SLIT before completing the recommended course of therapy,<sup>15</sup> and in a study of SLIT refill rates, prescription renewals occurred in only 44% of patients after 1 year of treatment, in 28% after 2 years of treatment, and in 13% after 3 years

of treatment.<sup>16</sup> However, these adherence rates are similar to those seen with SCIT and even with long-term pharmacotherapy for allergic disease and asthma.<sup>17</sup>

SLIT is currently approved for numerous allergens by the European regulatory authorities and is in wide use throughout Europe. In 2014, the US Food and Drug Administration announced approval of a 5-grass pollen sublingual tablet followed by approval of Timothy grass and ragweed pollen tablets. Although these are the only SLIT formulations currently approved for use in the United States, there has been and continues to be considerable "off-label" use of liquid allergen extracts that are approved only for skin testing or SCIT.<sup>2</sup> This is concerning because only a few of these agents have been studied for use by the sublingual route, sometimes without demonstrated efficacy, and no dosing standards have been established. Even fewer data are available to support use of these products as multi-allergen mixes as they are usually prescribed. Accordingly, considerably more research is needed before this off-label use of allergen extracts can be recommended.

In summary, rigorous studies of immunotherapy of all forms are clearly needed. The study by Virchow et al is a valuable contribution to the literature, especially given its focus on an important patient population with highly relevant end points. The work should not end here, as there is still a great deal of room for refinement in the practice of immunotherapy. As research continues and these therapies enter clinical practice, the goal should be to optimize each patient's immunotherapy regimen and disease control, taking personal preferences into account, and ideally to develop additional patient profiling using specific biomarkers to further personalize the use of these treatment options.

## ARTICLE INFORMATION

**Author Affiliation:** Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

**Corresponding Author:** Robert A. Wood, MD, Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, 600 N Wolfe St, CMSC 1102, Baltimore, MD 21287 (rwood@jhmi.edu).

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